

09997126

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NEWS 7 AUG 18 Simultaneous left and right truncation added to PASCAL
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Truncation
NEWS 9 AUG 18 Simultaneous left and right truncation added to ANABSTR
NEWS 10 SEP 22 DIPPR file reloaded
NEWS 11 SEP 25 INPADOC: Legal Status data to be reloaded
NEWS 12 SEP 29 DISSABS now available on STN
NEWS 13 OCT 10 PCTFULL: Two new display fields added
NEWS 14 OCT 21 BIOSIS file reloaded and enhanced
NEWS 15 OCT 28 BIOSIS file segment of TOXCENTER reloaded and enhanced

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MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
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FILE 'HOME' ENTERED AT 20:06:21 ON 02 NOV 2003

=> fil reg

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

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	ENTRY	SESSION
FULL ESTIMATED COST	0.21	0.21

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STRUCTURE FILE UPDATES: 31 OCT 2003 HIGHEST RN 611606-12-3
DICTIONARY FILE UPDATES: 31 OCT 2003 HIGHEST RN 611606-12-3

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2003

Please note that search-term pricing does apply when
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Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP
PROPERTIES for more information. See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

```
=> s atorvastatin hemi-calcium
      10 ATORVASTATIN
      5329 HEMI
      76661 CALCIUM
L1      2 ATORVASTATIN HEMI-CALCIUM
      (ATORVASTATIN(W)HEMI(W)CALCIUM)
```

	SINCE FILE	TOTAL
COST IN U.S. DOLLARS	ENTRY	SESSION
FULL ESTIMATED COST	13.06	13.27

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FILE COVERS 1907 - 2 Nov 2003 VOL 139 ISS 19
FILE LAST UPDATED: 31 Oct 2003 (20031031/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.

09997126

=> s l1 full
L2 127 L1

=> s l2 and form VIII
1308808 FORM
98646 VIII
91 FORM VIII
(FORM(W)VIII)
L3 1 L2 AND FORM VIII

=> d l3 ibib abs hitstr

L3 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:428715 CAPLUS
DOCUMENT NUMBER: 137:10960
TITLE: Novel crystal forms of atorvastatin hemicalcium and
processes for their preparation as well as novel
processes for preparing other forms
INVENTOR(S): Aronhime, Judith; Lidor-Hadas, Ramy; Niddam, Valerie;
Lifshitz, Revital; Ishai, Eti; Sambursky, Guy
PATENT ASSIGNEE(S): Teva Pharmaceutical Industries Ltd., Israel; Teva
Pharmaceuticals USA, Inc.
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002043732	A1	20020606	WO 2001-US44636	20011129
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TG			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
AU 2002017927	A5	20020611	AU 2002-17927	20011129
US 2002183378	A1	20021205	US 2001-997126	20011129
NO 2003002425	A	20030725	NO 2003-2425	20030528
PRIORITY APPLN. INFO.:			US 2000-250072P	P 20001130
			US 2001-267897P	P 20010209
			US 2001-281872P	P 20010405
			US 2001-312144P	P 20010813
			US 2001-326529P	P 20011001
			WO 2001-US44636	W 20011129

AB The present invention provides novel forms of atorvastatin designated Forms VI, VIII, IX, X, XI and XII and novel processes for their prepn. as well as processes for prepg. atorvastatin Forms, I, II, IV, V and amorphous atorvastatin. For example, 1.0 g (1.59x10⁻³ mole) of [R-(R*,R*)]-2-(4-fluorophenyl)-.beta.,.delta.-dioxane-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-tert-butylheptanoic ester was suspended in a 90% aq. soln. of acetic acid (10 mL) and heated to

50.degree.. The solvent was evapd. and the traces of acetic acid were removed by azeotropic distn. with toluene to obtain an oil with some toluene. This oil was dissolved in EtOH (10 mL) and water (2 mL) and then 5.5 equiv (8.4×10^{-3} mole, 622 mg) of $\text{Ca}(\text{OH})_2$ and tetra-Bu ammonium bromide (5%) were added. The reaction mixt. was heated at 50.degree. until the reaction was complete. Then a hot filtration was done under vacuum to remove the excess of $\text{Ca}(\text{OH})_2$ and the reaction mixt. was cooled to room temp. To this soln. water (50 mL) was added while stirring. The white ppt. was stirred at room temp. overnight, filtered under vacuum and dried at 65.degree. to give 145 mg (16%) of atorvastatin hemicalcium salt

Form VIII.

IT **134523-03-8P**, Atorvastatin hemicalcium

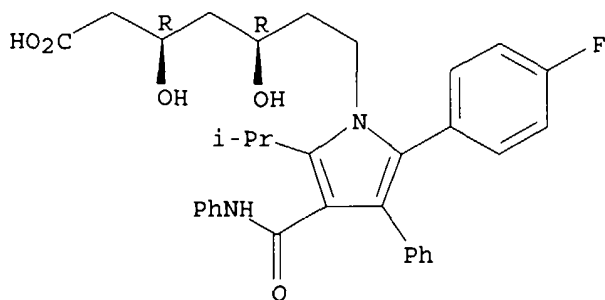
RL: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(prepn. of crystal forms of atorvastatin hemicalcium and its hydrate and solvates)

RN 134523-03-8 CAPLUS

CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-.beta.,.delta.-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-, calcium salt (2:1), (.beta.R,.delta.R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



●1/2 Ca

IT **344423-98-9P**, Atorvastatin hemicalcium trihydrate

RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

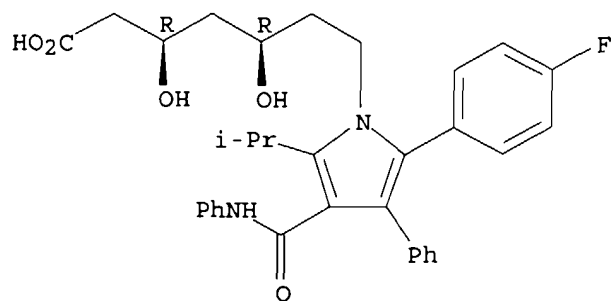
(prepn. of crystal forms of atorvastatin hemicalcium and its hydrate and solvates)

RN 344423-98-9 CAPLUS

CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-.beta.,.delta.-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-, calcium salt (2:1), trihydrate, (.beta.R,.delta.R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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● 1/2 Ca

● 3/2 H₂O

REFERENCE COUNT:

3

THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS
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=> fil reg

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

0.21

0.21

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DICTIONARY FILE UPDATES: 31 OCT 2003 HIGHEST RN 611606-12-3

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2003

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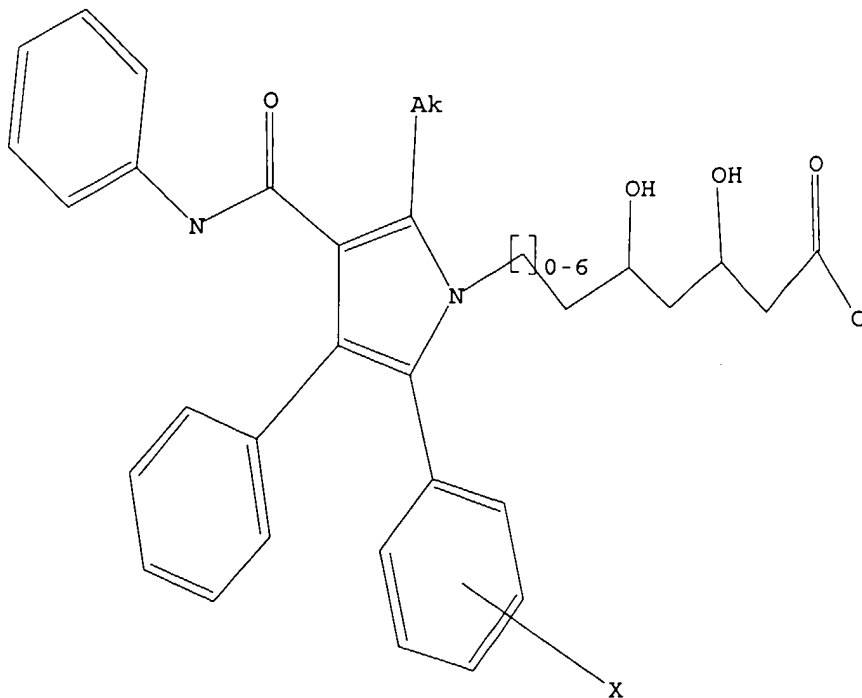
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<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

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L1 STRUCTURE UPLOADED

=> d
L1 HAS NO ANSWERS
L1 STR



Structure attributes must be viewed using STN Express query preparation.

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=> s l1 sss sam

SAMPLE SEARCH INITIATED 20:17:32 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 7 TO ITERATE

100.0% PROCESSED 7 ITERATIONS 5 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 7 TO 298
PROJECTED ANSWERS: 5 TO 234

L2 5 SEA SSS SAM L1

=> s l1 full

FULL SEARCH INITIATED 20:17:35 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 98 TO ITERATE

100.0% PROCESSED 98 ITERATIONS 65 ANSWERS
SEARCH TIME: 00.00.01

L3 65 SEA SSS FUL L1

=> fil caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
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FILE COVERS 1907 - 2 Nov 2003 VOL 139 ISS 19
FILE LAST UPDATED: 31 Oct 2003 (20031031/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l3 full

L4 1020 L3

09997126

=> s l4 and peaks?

146370 PEAKS?

L5 3 L4 AND PEAKS?

=> d l5 1-3 ibib abs hitstr

L5 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2003:678785 CAPLUS

DOCUMENT NUMBER: 139:202534

TITLE: Novel crystal forms of atorvastatin hemi-calcium and processes for their preparation, as well as novel processes for preparing atorvastatin hemi-calcium forms I, VIII and IX

INVENTOR(S): Tessler, Limor; Aronhime, Judith; Lifshitz-Liron, Revital; Maidan-Hanoch, Dalia; Hasson, Nir

PATENT ASSIGNEE(S): Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.

SOURCE: PCT Int. Appl., 34 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003070702	A1	20030828	WO 2003-US5384	20030219
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 2002-357181P P 20020215

US 2002-425325P P 20021112

AB Solid cryst. atorvastatin hemi-calcium, and solvates, which are characterized by a powder X-ray diffraction pattern having **peaks** at 9.3 and 9.5+0.2 degrees two-theta are prepd.

IT 134523-03-8, Atorvastatin hemi-calcium

RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

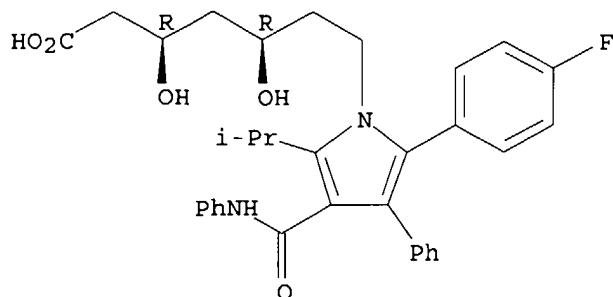
(prepn. of novel crystal forms of atorvastatin hemi-calcium)

RN 134523-03-8 CAPLUS

CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-.beta.,.delta.-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-, calcium salt (2:1), (.beta.R,.delta.R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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● 1/2 Ca

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2001:4785 CAPLUS

DOCUMENT NUMBER: 134:202384

TITLE: A Four-Column Parallel Chromatography System for Isocratic or Gradient LC/MS Analyses

AUTHOR(S): van Pelt, Colleen K.; Corso, Thomas N.; Schultz, Gary A.; Lowes, Stephen; Henion, Jack

CORPORATE SOURCE: Advanced BioAnalytical Services Inc., Ithaca, NY, 14850, USA

SOURCE: Analytical Chemistry (2001), 73(3), 582-588

CODEN: ANCHAM; ISSN: 0003-2700

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A novel approach to parallel liq. chromatog./tandem mass spectrometry (LC/MS/MS) analyses for pharmacokinetic assays and for similar quant. applications is presented. Modest modifications render a conventional LC/MS system capable of analyzing samples in parallel. These modifications involve the simple incorporation of three valves and four LC columns into a conventional system composed of one binary LC pumping system, one autosampler, and one mass spectrometer. An increase in sample throughput is achieved by staggering injections onto the four columns, allowing the mass spectrometer to continuously analyze the chromatog. window of interest. Using this approach, the optimized run time is slightly greater than the sum of the widths of the desired **peaks**. This parallel chromatog. unit can operate under both gradient and isocratic LC conditions. To demonstrate the utility of the system, atorvastatin, five of its metabolites, and their deuterated internal stds. (IS) were analyzed using gradient elution chromatog. conditions. The results from a pre-study assay evaluation (PSAE) tray of stds. and quality control (QC) samples from extd. spiked human plasma are presented. The relative std. deviation and the accuracy of the QC samples did not exceed 8.1% and 9.6%, resp., which is well within the acceptance criteria of the pharmaceutical industry. For this particular anal., the parallel chromatog. system decreased the overall run time from 4.5 to 1.65 min and, therefore, increased the overall throughput by a factor of 2.7 in comparison to a conventional LC/MS/MS anal. method.

IT 134523-00-5, Atorvastatin

RL: ANT (Analyte); BPR (Biological process); BSU (Biological study,

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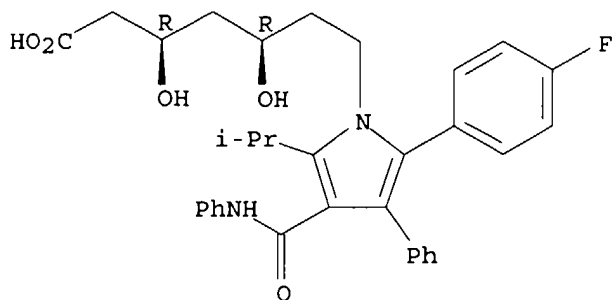
unclassified); ANST (Analytical study); BIOL (Biological study); PROC
(Process)

(four-column parallel chromatog. system for isocratic or gradient LC/MS
analyses)

RN 134523-00-5 CAPLUS

CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-.beta.,.delta.-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-, (.beta.R,.delta.R)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **214217-86-4**, 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-.beta.,.delta.-dihydroxy-4-[[[(2-hydroxyphenyl)amino]carbonyl]-5-(1-methylethyl)-3-phenyl]-, (.beta.R,.delta.R)- **214217-88-6**

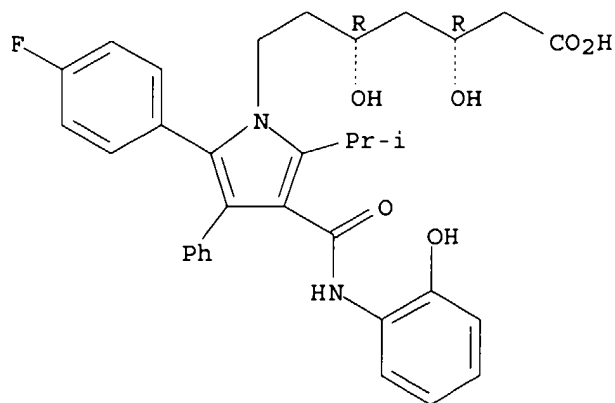
RL: ANT (Analyte); BSU (Biological study, unclassified); MFM (Metabolic formation); ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative)

(four-column parallel chromatog. system for isocratic or gradient LC/MS analyses)

RN 214217-86-4 CAPLUS

CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-.beta.,.delta.-dihydroxy-4-[[[(2-hydroxyphenyl)amino]carbonyl]-5-(1-methylethyl)-3-phenyl]-, (.beta.R,.delta.R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

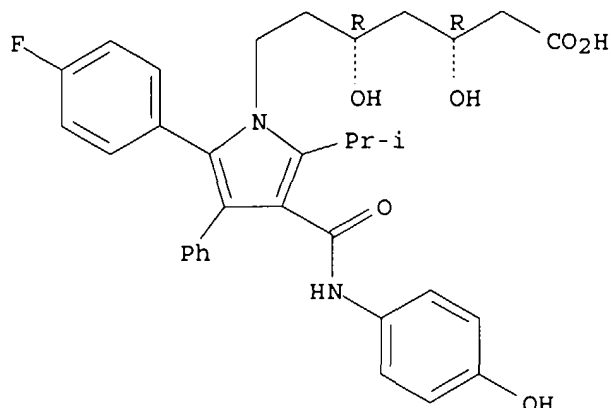


RN 214217-88-6 CAPLUS

CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-.beta.,.delta.-dihydroxy-4-[[[(4-hydroxyphenyl)amino]carbonyl]-5-(1-methylethyl)-3-phenyl]-, (.beta.R,.delta.R)- (9CI) (CA INDEX NAME)

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Absolute stereochemistry.



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1999:8790 CAPLUS

DOCUMENT NUMBER: 130:191350

TITLE: Development and validation of a high-performance liquid chromatography tandem mass spectrometry assay for atorvastatin, o-hydroxyatorvastatin, and p-hydroxyatorvastatin in human, dog, and rat plasma

AUTHOR(S): Bullen, William W.; Miller, Ronald A.; Hayes, Roger N.

CORPORATE SOURCE: Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, Ann Arbor, MI, 48105, USA

SOURCE: Journal of the American Society for Mass Spectrometry (1999), 10(1), 55-66

CODEN: JAMSEF; ISSN: 1044-0305

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A liq. chromatog./mass spectrometric method to quantitate atorvastatin (AT) and its active metabolites o-hydroxy (o-AT) and p-hydroxy (p-AT) atorvastatin in human, dog, and rat plasma was validated. The method consisted of washing plasma samples at high pH with Et2O and subsequently extg. the analytes and 2 internal stds., [d5]-AT and [d5]-o-A, from acidified plasma with Et2O. The org. layer was evapd. to dryness and the residue reconstituted in NH4OAc (20 mM, pH 4.0)-MeCN-iso-PrOH (60:40:1). Chromatog. sepn. of analytes was achieved by using a YMC J'Sphere H80 (C-18) 150 x 2 mm, 4 .mu.m particle size, column with a mobile phase consisting of MeCN-0.1% HOAc (70:30). Analytes were detected by using tandem mass spectrometry. Sample introduction and ionization were by electrospray ionization in the pos. ion mode. The method proved suitable for routine quantitation of AT, o-AT, and p-AT over the concn. range 0.250-25.0 ng/mL. Approx. retention time ranges of p-AT, o-AT, [d5]-o-AT, AT, and [d5]-AT were 2.27, 3.36, 3.54, 4.12, and 4.65 min, resp. No **peaks** interfering with quantitation were obsd. throughout the validation processes. Mean recoveries of AT, o-AT, and p-AT from plasma ranged 100%-107%, 70.6%-104%, and 47.6%-85.6%, resp. Mean recoveries of the [d5]-AT and [d5]-o-AT internal stds. ranged 98.0%-99.9% and 97.3%-97.9%, resp. Interassay precision, based on the percent relative

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deviation for replicate quality controls for AT, o-AT, and p-AT, was .ltoreq.7.19%, 8.28%, and 12.7%, resp. Interassay accuracy for AT, o-AT, and p-AT was .+-.10.6%, 5.86%, and 15.8%, resp. AT, o-AT, and p-AT in human, dog, and rat plasma quality control samples were stable to 3 freeze-thaw cycles. AT, o-AT, and p-AT were stable when frozen for 127, 30 and 270 days in human, dog, and rat plasma quality control samples, resp. Human plasma quality control samples contg. AT, o-AT, and p-AT were stable for .gtoreq.4 days at ambient room temp. and 37.degree.. The lower limit of quantitation for all the analytes was 0.250 ng/mL for a 1.0-mL sample aliquot.

IT 134523-00-5, Atorvastatin

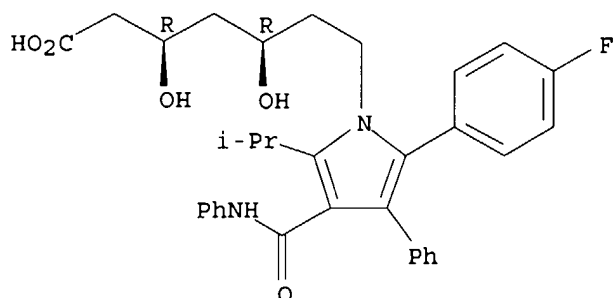
RL: ANT (Analyte); ANST (Analytical study)

(detn. of atorvastatin, o-hydroxyatorvastatin, and p-hydroxyatorvastatin in human, dog, and rat plasma by HPLC and tandem mass spectrometry)

RN 134523-00-5 CAPLUS

CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-.beta.,.delta.-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-, (.beta.R,.delta.R)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 214217-86-4, o-Hydroxyatorvastatin 214217-88-6, p-Hydroxyatorvastatin

RL: ANT (Analyte); BSU (Biological study, unclassified); MFM (Metabolic formation); ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative)

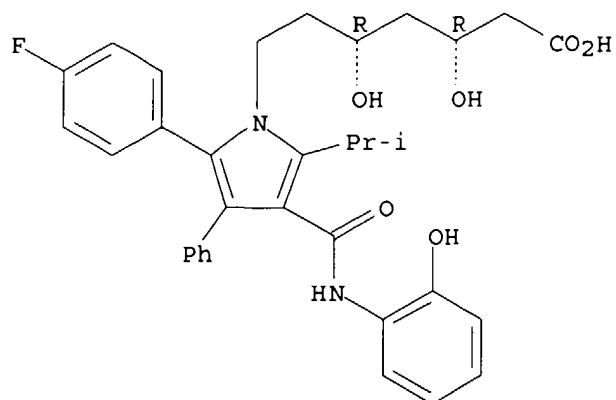
(detn. of atorvastatin, o-hydroxyatorvastatin, and p-hydroxyatorvastatin in human, dog, and rat plasma by HPLC and tandem mass spectrometry)

RN 214217-86-4 CAPLUS

CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-.beta.,.delta.-dihydroxy-4-[[[(2-hydroxyphenyl)amino]carbonyl]-5-(1-methylethyl)-3-phenyl-, (.beta.R,.delta.R)-(9CI) (CA INDEX NAME)

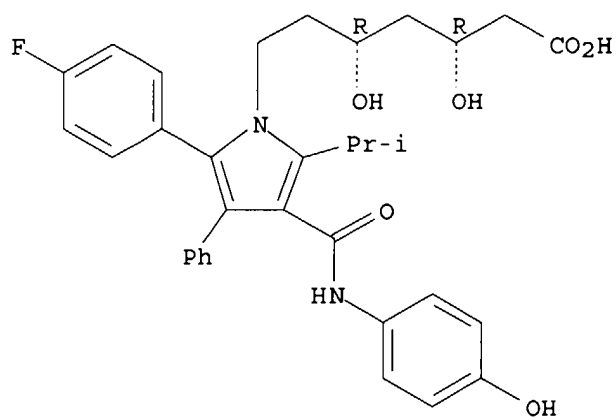
Absolute stereochemistry.

09997126



RN 214217-88-6 CAPLUS
CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-.beta.,.delta.-dihydroxy-4-
[[(4-hydroxyphenyl) amino] carbonyl]-5-(1-methylethyl)-3-phenyl-,
(.beta.R,.delta.R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT